Journal of Saudi Chemical Society (2014) **18**, 47–51

King Saud University

Journal of Saudi Chemical Society

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ORIGINAL ARTICLE

Mechanochemistry: An efficient method of solvent-free synthesis of 3-amino-2,4-dicarbonitrile-5-methylbiphenyls

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Received 28 December 2010; accepted 24 May 2011
Available online 30 May 2011

KEYWORDS

3-Amino-2,4-dicarbonitrile-5-methylbiphenyls;
Aromatic aldehydes;
Malononitrile;
Acetone;
NaOMe

Abstract 3-Amino-2,4-dicarbonitrile-5-methylbiphenyls are synthesized by a three-component reaction of aromatic aldehydes, malononitrile, and acetone in the presence of catalytic NaOMe under grindstone method. The yields are excellent; the procedure is simple, efficient, and environmentally benign; and all the reactions go to completion within 2–3 min.

1. Introduction

In the beginning of the nineteenth century, a shift in emphasis on organic synthesis is apparent with the desire to develop environmentally benign routes to a number of biologically active molecules using non-toxic reagents, solvents, and catalysts (Anastas and Williamson, 1998). Due to the deterioration of the environment, since 1990's, use of *green protocols* in the chemical reactions has become the trend setter. One of the methods belonging to such a protocol is *grindstone* method. This mechanically activated solvent-free reaction helps in reducing the toxic waste produced, and therefore, becomes less harmful to the environment. Solvent-less organic reactions based on grinding of two macroscopic particles together mostly involves the formation of a liquid phase prior to the reaction, i.e. formation of an eutectic melt of uniform distribution where the reacting components being in close proximity react in a controlled way (Kumar et al., 2008). *Grindstone* method can even set off some reactions that cannot be carried out under traditional conditions (Wang et al., 2003). The wide application of *grindstone* method is evident from the fact that, many reactions like Reformatsky reaction (Tanaka et al., 1991), Aldol condensation (Toda et al., 1990), Dieckmann condensation (Toda et al., 1998), Knoevenagel condensation (Ren et al., 2002), Biginelli reaction (Ren et al., 2004), synthesis of carbamates (Pathak et al., 2008), and others (Modarresi-Alam et al., 2007) are possible by just grinding the substrates in the presence of a suitable catalyst.

On the other hand, biaryl moiety is present in the molecules of current interest including natural products, polymers, advanced materials, liquid crystals, and a number of biologically active molecules (Bringmann et al., 1990). Moreover, 2,6-dicyano-aryl-anilines belong to a typical A–D–A (acceptor–

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Peer review under responsibility of King Saud University.
doi:10.1016/j.jscs.2011.05.012

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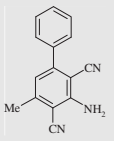
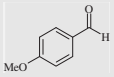
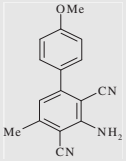
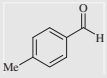
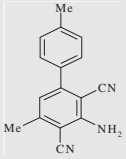
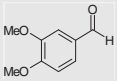
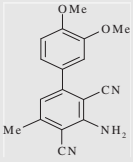
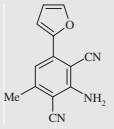
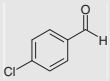
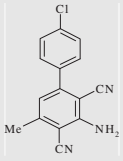
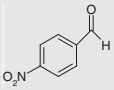
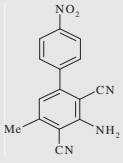
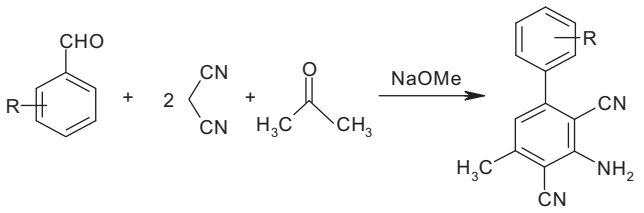
Table 1 NaOMe catalyzed synthesis of biaryls from aldehydes, malononitrile and acetones under grindstone method.

Entry	Aldehyde	Product	Time (min)	Yield[a] (%)	Melting point (°C)[b] Found	Reported
a			2	95	187	188–190
b			2	97	189	190
c			3	94	219	200
d			3	95	222	224–225
e			3	90	196	198–199
f			2	95	237	236–240
g			3	91	228–230†	–

[a] Isolated yields.
[b] Rong et al., 2008; Cui et al., 2005; Raghukumar et al., 2001.
† Novel compound.

donor–acceptor) type of compounds; which have been used recently in the artificial photosynthetic systems (Fox and Chanon, 1988). A number of procedures have been developed for the synthesis of these compounds using a variety of protocols. The typical method for these compounds is *via* a cross-coupling of aryl metals with aryl halides (aryl iodides, bromides, and chlorides) mediated by transition-metal catalysts (Negishi, 2002; Hassan et al., 2002); a [2 + 2 + 2]



Scheme 1 Solvent-free synthesis of 3-amino-2,4-dicarbonitrile-5-methylbiphenyls. R = H, 4-OMe, 4-Me, 3,4-di-OMe, 4-Cl, 4-NO_2, furfuryl,

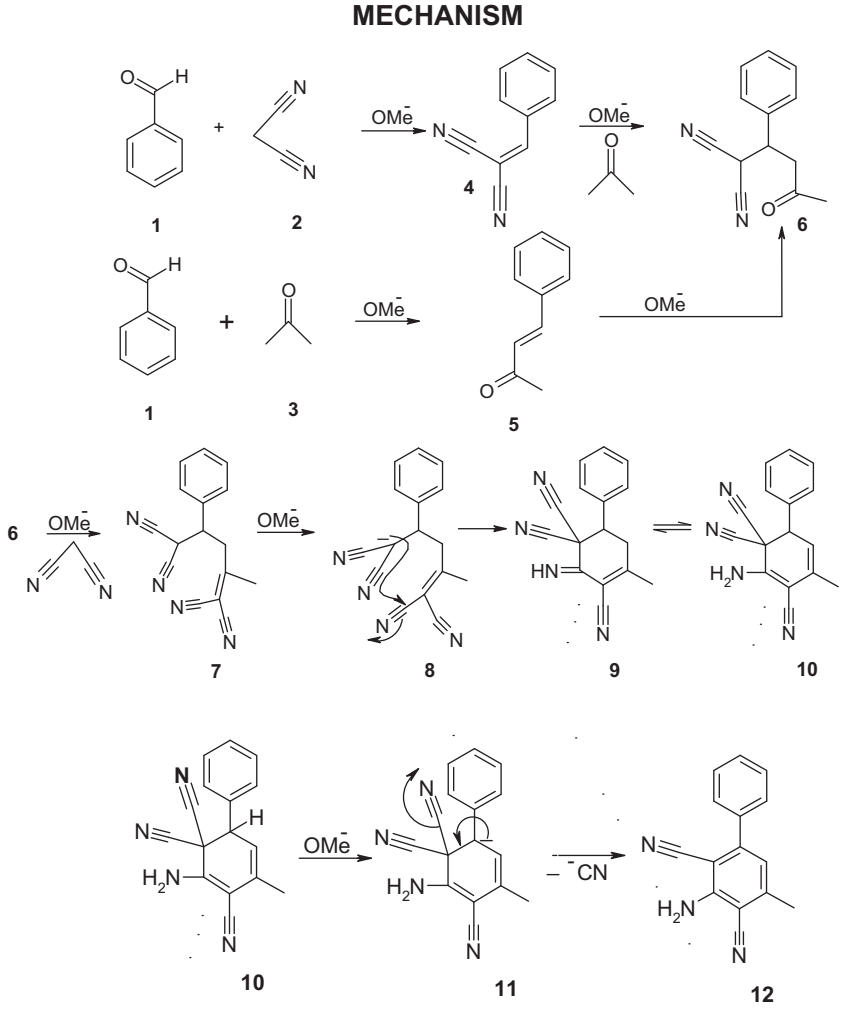
co-cyclization (Sato et al., 1999), Ullmann coupling (Bringmann et al., 1990), the Stille reaction (Farina, 1996), and use of Grignard reagents (Bumagin and Luzikova, 1997). Recently, a few one-pot three-component reactions of aromatic aldehydes, malononitrile, and acetone in the presence of basic catalysts (Rong et al., 2008; Cui et al., 2005; Raghukumar et al., 2001) have been reported to give the desired products. However, the reported methods such as coupling of aryl metals with aryl halides entail the use of expensive catalysts, excess solvent, harsh reaction conditions, and costly starting materials which significantly limit their industrial applications. The one-pot reactions though follow a significant protocol, give lesser yields (piperidine catalyzed reaction (Raghukumar et al., 2001) is not applicable to benzaldehyde). Therefore, it is essential to explore a simple, green, alternative method for the synthesis of substituted biphenyls.

In continuation of our work on developing simple and environmentally benign reaction catalysts for the synthesis of biologically active molecules such as amidoalkyl-2-naphthols (Datta and Pasha, 2010), β-enaminones and β-enaminoesters (Datta and Pasha, 2011), β-acetamido-β-aryl-propionones (Pasha et al., 2007a), 5-Arylmethylidene-2-phenyloxazol-4-ones (azalactones) (Reddy and Pasha, 2010), α-aminonitriles (Pasha et al., 2007b) and 2-aminobenzochromene (Pasha and Jayashankara, 2007), herein, we report a simple, efficient and cost-effective one-pot method for the synthesis of 3-amino-2,4-dicarbonitrile-5-methylbiphenyls from aromatic aldehydes; malononitrile and acetone using sodium methoxide as a catalyst under grindstone method.

2. Experimental

2.1. Materials and methods

All aromatic aldehydes, acetone and malononitrile were commercial products and were used without further purification.



Scheme 2 Formation of 3-amino-2,4-dicarbonitrile-5-methylbiphenyls.

Yields refer to isolated products. Melting points were measured on a Büchi B-540 apparatus; IR and ^{1}H-NMR spectra were recorded on Nicolet 400D FT-IR and Bruker AMX (400 MHz) spectrophotometers, respectively. The IR spectra were taken as KBr pellets. LC–MS was performed on an Agilent Technologies 1200 series instrument and GC–MS on a SHIMADZU QP 5050A instrument.

2.2. General procedure

Malononitrile (10 mmol), aromatic aldehyde (5 mmol), acetone (5 mmol), and NaOMe (3 mmol) were taken in a pestle and ground well for 2–3 min using a mortar. After completion of the reaction (TLC), water (10 ml) was added and the solid thus separated was filtered, washed repeatedly with water to get the corresponding biaryl derivatives. Analytical grade samples were obtained by recrystallization from aq. alcohol. Yields and physical constants of all the products prepared by this procedure are presented in the Table 1.

3. Results and discussion

In an initial endeavor, 5 mmol of benzaldehyde was treated with 10 mmol of malononitrile and 10 ml of acetone and refluxed without any catalyst. Even after 5 h, the required product was not noticed. As the yields were low, we planned to use a slightly better, easy to handle and more basic NaOMe which was prepared from MeOH-Na metal and used for the reaction. In the presence of 1 mmol NaOMe and after 4 h only 55% of the expected product was obtained. We tried to increase the yield by adding excess of malononitrile but the yield remained the same. In order to improve the yield we tried grindstone method. In this method, the yield started improving, and maximum yield could be achieved by increasing the amount of NaOMe to 3 mmol. We observed that, during grinding the reaction mixture was in partial liquid state, which gradually solidified. The reaction completed in 2–3 min, and the 3-amino-2,4-dicarbonitrile-5-methylbiphenyl was obtained in 95% yield. Recently, Tu et al. used NaOH (Rong et al., 2008) as a reagent (1.5 equivalents) for the synthesis of substituted biphenyls (yield 72–81%). From the mechanism we can observe that 3 mmol of NaOMe is sufficient to obtain the desired product because the catalyst is reformed during the reaction and helps in completion of the reaction.

To see the applicability of this reaction, various aromatic aldehydes were used according to the Scheme 1 and the results of this study are presented in Table 1. It is clear from the table that the aromatic aldehydes bearing electron-withdrawing and electron-donating groups performed equally well in this reaction and give excellent yield of the products within 2–3 min. All the 3-amino-2,4-dicarbonitrile-5-methylbiphenyls synthesized by this procedure are characterized by comparison of their melting point with the reported melting points, and by comparison with samples prepared by known procedures on TLC and/or from their IR, ^{1}H-NMR and mass spectral analysis.

The novel product 3-amino-2,4-dicarbonitrile-4′-nitro-5-methylbiphenyl (**4g**) in its IR spectrum showed the stretching vibration for C≡N at 2221.84 cm^{-1} as a sharp peak and the NH_2 signal appeared at 3257.55 cm^{-1}. The ^{1}H-NMR spectrum of **4g** showed a singlet for CH_3 protons at 2.385 ppm, a broad signal for NH_2 protons at 6.99 ppm, and a singlet for aromatic C-6 proton at 7.259 ppm; C-2′ and C-6′ proton gave a doublet between 7.420 and 7.441 ppm (J = 8.4 Hz, 2H) and C-3′ and 5′ protons appeared as a doublet between 7.769 and 7.790 ppm (J = 8.4 Hz, 2H). The mass spectral analysis showed m/z 277.0 for M+.

4. Mechanism

The aldehyde is expected to undergo a Knoevenagel condensation with malononitrile to give **4**, followed by the Aldol condensation with acetone to give the intermediate **6**. At the same time aldehyde may also undergo an Aldol condensation followed by the Knoevenagel condensation simultaneously with malononitrile to give **6** through the intermediate **5** [both the intermediates **4** and **5** have been identified as the by-products by GC]. Intermediate **6** may further undergo a second Knoevenagel condensation with another molecule of malononitrile and give intermediate **7**. This intermediate **7** may subsequently get cyclized to form a non-aromatic six member ring intermediate **10**. Later on, in the presence of sodium methoxide **10** may undergo dehydration to form the desired biaryl derivative as shown in Scheme 2.

5. Conclusion

In conclusion, we have successfully synthesized 3-amino-2,4-dicarbonitrile-5-methylbiphenyls by the condensation of aromatic aldehydes, malononitrile and acetone in the presence of catalytic amounts of NaOMe, under solvent-free *grindstone* method. The mildness of the conversion, experimental simplicity, compatibility with various functional groups, excellent yields, short reaction times and the easy workup procedure makes this protocol an attractive and user friendly alternate method for the synthesis of substituted biphenyls. To increase the scope of the present reaction on industrial scale use of 'high speed ball mills' is recommended (Gao and Wang, 2008).

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